UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,964	02/10/2004	Jia-Hwa Fang	PP16502.015	1609

7590 02/18/2010

Alisa Harbin, Esq.
Novartis Vaccines and Diagnostics, Inc.
Intellectual Property - R440
P. O. Box 8097
Emeryville, CA 94662

EXAMINER	
FUBARA, BLESSING M	

ART UNIT	PAPER NUMBER
1618	

MAIL DATE	DELIVERY MODE
02/18/2010	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/775,964	FANG ET AL.	
	Examiner	Art Unit	
	BLESSING M. FUBARA	1618	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 November 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *34-42 and 62-76* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *34-42 and 62-76* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The examiner acknowledges receipt of request extension of time, amendment remarks filed 11/12/09. Claims 34, 36, 37, 39, 40 and 62-67 are amended. Claims 34-42 and 62-76 are pending.

Response to Arguments

Previous rejections that are not reiterated herein are withdrawn.

Claim Rejections - 35 USC § 103

1. Claims 34-42 and 62-76 are rejected under 35 U.S.C. 103(a) as being unpatentable over Levy et al. (US 6,395,253) in view of O'Hagan et al. (WO 00/50006) or Van Nest (US 2001/0046967) for reasons of record and with a modification to address the amendment to the claims where the amendment now states micro-particle emulsion in the claims.

2. LEVY discloses preparation of microspheres that contain DNA or RNA as the bioactive agent (column 4, lines 31, 54 and 55). LEVY prepares a double emulsion of water-in-oil-in-water emulsion by using a condensing agent in one phase and the method comprises the steps of: "(a) dissolving at least one polymer in a water-immiscible organic solvent to yield an organic phase; (b) dissolving a polyanionic bioactive agent in aqueous solution to yield a first aqueous phase; (c) emulsifying the organic and first aqueous phases to yield a first milky emulsion; (d) dissolving a condensing agent in aqueous solution to yield a second aqueous phase; (e) emulsifying the first milky emulsion and the second aqueous phase to yield a second milky emulsion; and (f) removing the organic solvent from the second milky emulsion to yield microspheres containing condensed polyanionic bioactive agent with the emulsion meeting

claims 34, 35 and 36-39. "The removal of the organic solvent in the final step is preferably by means of evaporation," in one illustrative embodiment (column 4, lines 44 and 45). DNA and RNA are macromolecules and are polynucleotides meeting the requirements of claims 74-76. The concept of microspheres meets the microparticle limitation of claims 34, 37, 39, 42, 62, 65-70. Regarding the recitation that the microparticles are not subjected to washing step, it is noted that while the examples in Levy disclose a wash step, the basic preparation disclosed by Levy in section 4.2 does not state a wash step but rather that the microspheres are collected by ultracentrifugation and the alternative protocol disclosed in 4.6 and the comprising language is open. Levy uses 0.1% detergent (SDS in this case). There is no demonstration in applicants' specification that not subjecting the microparticles to a washing step provides unusual/unexpected results to the microparticles. The claims do not recite amount of detergent added to make the microparticle in the emulsion. Claims 34, 36, 37, 39 and 62-70 now recite that the composition is a micro-particle suspension. Levy teaches emulsion and present in the emulsion are micro-spheres that meet the limitation of micro-particle. An emulsion is a special type of suspension. A micro-particle suspension is a suspension of micro-particles and the suspension of micro-spheres in the emulsion/suspension meets the limitation of micro-particle suspension. Combining the phases in Levy meets the mixing step of claims 34 and 37; adsorption of macromolecule onto micro-particles would take place when macromolecules and micro-particle are placed together so that the macromolecules are adsorbed onto the particles, thus meeting the adsorption requirement of claims 34, 36, 37, 39 and 62-70.

3. Regarding claim 36, which is directed to the process of cross-flow filtration, it is noted that in the cross-flow filtration process of the examined application, four liters of deionized water

(Example 5) is used to remove the detergents and this appears to be equivalent to washing so that the cross-filtration step of the claim 34 reads on optional wash step of one of embodiments of Levy at column 13, line 5; at column 18, line 42 (washed with tris-EDTA); at column 20, line 2 (cells washed with PBS buffer). There is also no demonstration that the cross-filtration step performed after removing the organic solvent provides unusual results; Levy discloses filtration as one of the steps. The filtration step in Levy meets the filtration step in claims 34 and 37.

4. Regarding the ratio of lactide to glycolide, it is noted that there is no demonstration by applicants that the recited ratio provides unusual/expected results. The silence of Levy on the ratio of lactide to glycolide is an indication that the lactide/glycolide can be used in any desired ratio that would be effective as a condensing agent for the DNA or RNA macromolecules. Levy also teaches polypeptide (column 4, line 64) meeting claim 72 and the SDS meets claim 71.

5. Regarding claims 68-70, Levy in one of the embodiments does not wash the product but removes the solvent from the emulsion by evaporation so that that the detergent is not removed or washed off (column 12, lines 58-67).

6. Levy uses SDS detergent. While Levy does not specifically state the presence of bound detergent in the amounts recited in the claims, it is noted that Levy does not specifically state that the microspheres/particles formed are free of detergent; and it flows from one of the embodiment that does not use a wash step but evaporates off the organic solvent (column 12, lines 58-67) that the detergent is not removed and as such, the microparticles would have detergent associated. However, while Levy teaches SDS and TWEEN, Levy does not disclose the use of cetyl trimethyl ammonium bromide (CTAB) detergent. But emulsions containing microparticles comprising macromolecules such as polynucleotides and polypeptides, polymers such as poly(α-

hydroxy acid), a polyhydroxy butyric acid, polycaprolactone, polyorthoester, polyanhydride and polycyanoacrylate, and cationic detergents such as CTAB are known in the art (see O'Hagan at page 7, last full paragraph, pages 8-11; Tables 19A and 19B; and page 2, 4th full paragraph). Thus O'Hagan is relied upon for a teaching that the specific CTAB detergent can be used with PLG in an emulsion with macromolecules. CTAB and the SDS meet the detergent limitations of claims 38, 40, 68, 71. Further also, Van Nest discloses that polynucleotides may be delivered in vehicles such as liposomes or emulsions made with cationic lipids or polymers, such as 1,2-dioleoyl-1,2,3-trimethylammoniopropane (DOTAP), cetyltrimethylammonium bromide (CTAB) or polylysine (see paragraphs [0101], [0091], [0090], [0088] and [0086]). Therefore, taking the teachings of the references together, one having ordinary skill in the art at the time at the invention was made would have reasonable expectation of success that including the detergent CTAB in the double emulsion of Levy would produce emulsion whose particles would effectively adsorb polynucleotides and polypeptides that would be expected to release/deliver the polynucleotide and the polypeptide as desired.

Response to Arguments

7. Applicant's arguments filed 11/12/09 have been fully considered but they are not persuasive.

8. Applicant argues that Levy does not teach or suggest adsorption of macromolecules to micro-particles but Levy is rather directed to micro-encapsulation of macro-molecules into polymeric micro-spheres.

9. Response: Claims 34 and 37 say that the biologically active macromolecule is adsorbed to micro-particles in said suspension. Thus, by implication, the biologically active

macromolecule is adsorbed to the micro-particles when the biologically active macromolecule and the micro-particles come in contact. The examiner acknowledges that Levy does not categorically say that the macromolecules are adsorbed to the micro-sphere/micro-particle. Although, applicant contends that Levy produces micro-spheres containing bioactive agent and that according to the production process, the macromolecules cannot be adsorbed to the particles, the process by which the micro-particles of Levy is prepared does not exclude the adsorption of the biologically active macromolecule to the micro-particle. The rejection is not made under 35 USC 102 where the steps have to be followed exactly in order to anticipate the claims. But, the order of putting together the same components to arrive at the same product, in this case micro-particle suspension is not inventive over the prior art reference that combines the same components to prepare the same product. Selection of any order of performing process steps is prima-facie obvious in the absence of new and unexpected results, see *Ex parte Rubin* , 128 USPQ 440 (Bd. App. 1959), *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) and *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930). In the instant case, applicant has not shown that the biologically active macromolecule is not adsorbed to the micro-sphere.

10. Applicant argues that there is no reason for the ordinary skilled artisan to incubate or bring together or contact the micro-particles of Levy with biologically active macromolecule.

11. Response: The examiner appreciates applicant's point of view that it is unnecessary for the ordinary skilled artisan to go about incubating or contacting ... biologically active macromolecule with the micro-particles of Levy. The examiner also notes that the biologically active macromolecule and the micro-particles are in contact already and there is no force, chemical or physical, or nothing that precludes the biologically active macromolecule from

adsorbing to the micro-particles. Even as applicant says that the biologically active macromolecule such as DNA is positioned in the inner phase of the a double water-in-oil-in-water emulsion, the encapsulated biologically active macromolecule has contact with the micro-particle and the adsorption is not precluded. The method steps of Levy differs from the method steps of the claims and in a rejection under 35 USC 103, the method steps are permitted to be different (see *Ex parte Rubin* , 128 USPQ 440 (Bd. App. 1959), *In re Burhans*, 154 F.2d 690, 69 USPQ 330 (CCPA 1946) and *In re Gibson*, 39 F.2d 975, 5 USPQ 230 (CCPA 1930)).

12. Applicant also argues that Levy does not describe as does the invention that 10-90% of the total detergent in the microparticle composition is bound to the microparticles and the remainder unbound; and that the specification at paragraph [0011] and onwards shows that the inventors "have unexpectedly found that adsorption of macromolecules to micro-particles can be improved by ensuring that that detergent is made available for forming complex with the macromolecules at the time of adsorption."

13. Response: Paragraph [0011] says nothing about what is expected and what is unexpected. It is true that paragraph [0011] states that adsorption of macromolecules to micro-particles is improved by ensuring that detergent is made available and the claims says that 10-90% of the detergent is bound, however, the detergent in Levy is also available; the detergent in the embodiment where a wash cycle is not employed would mean the presence of large amounts of detergent. The claims and the prior art references use the same biologically active macromolecule and the same polymers for the micro-particles so that the interaction between the biologically active macromolecule and the micro-particle would occur in both cases in view of

the polymeric micro-particle and the presence of surfactant. Levy does not disclose that 100% of the detergent used in the composition is washed of.

14. The examiner also disagrees with the applicant with respect to the amount of the detergent present in Levy. The USPTO does not have the laboratories to ascertain if the micro-particles of Levy have detergents and what percent of the of the original detergent is present in the micro-particles. Applicant has not determined that either less than 10-90% detergent is bound to the microparticles in the Levy art or that less than 10-90% is unbound of the total detergent in the microparticles. The examiner agrees with applicant that Levy is silent on whether the detergent is bound or unbound. But, applicant has not provided or disclosed or claimed specific methods that ensure binding and one that does not ensure binding.

15. Applicant argues that the claimed invention has embodiments in which the micro-particles are subjected to filtration to remove excess detergent and other embodiments in which the micro-particle suspension is not subjected to a step of removing excess detergent and that the ultra-filtration step in levy constitutes detergent removal step and that such a step would be excluded by the claims.

16. Response: From the foregoing applicant says that there are two embodiments, one where excess detergent is removed and another where excess detergent is not removed. In Levy, therefore, the removal of the excess detergent, noting that excess detergent is a relative term, meets the embodiment of the claims removing excess detergent and the situation in Levy, where the basic preparation disclosed in section 4.2 does not state a wash step is the scenario when the embodiment of not removing excess detergent is met, again keeping in mind that "excess" is relative.

17. Applicant also argues that the disclosure of 0.1% SDS is not relevant to the claimed invention because 0.1% SDS is used in dissolution studies.

18. Response: While the examiner concedes that 0.1%SDS is used in the characterization of condensed DNA, the examiner also notes that Levy uses SDS/detergent/surfactant in the emulsion (column 12, lines 47-57) with the emulsifying agent used at 0.01-20%. The reference to MPEP 2144.04 [R-6] IV C. was not an attempt by the examiner to justify the use of SDS in the disclosure of Levy, rather it was to convey that selection of method steps is prima facie and the examiner is not doing any of those things the applicant alleges the examiner of doing.

19. The examiner also acknowledges applicant's indication that no unusual/unexpected results has been made.

20. Applicant points to the advantages of cross-filtration over regular filtration. However, the examiner agrees that Levy does not teach cross-filtration, but it is noted that the cross-filtration is, in the examiner's opinion and in the present case achieves the same effect, in that four liters of deionized water (instant Example 5) is used to remove the detergents and this appears to be equivalent to washing so that the cross-filtration step of claim 34 reads on optional wash step of one of the embodiments of Levy at column 13, line 5; at column 18, line 42 (washed with tris-EDTA); at column 20, line 2 (cells washed with PBS buffer).

21. Applicant continues to argue the importance of 10-90% detergent, but the 10-90% detergent is a very broad range that is not patentable over a teaching where 0.01% to about 20% detergent is used and when there is no wash step, the amount of detergent present in the product would be close to about 0.1% to about 20%.

22. Applicant argues that there cannot be any adsorption in Levy.

23. Response: The examiner disagrees because both the claims and the reference teach micro-particles that have macromolecules and detergent and polyydroxy acid (lactide/glycolide) so that the forces that influence adsorption would be the same in both instances, whether it is in the inside of the particle or on the outside of the particle. The 10-90% is related to 10-90% of the total detergent used in the composition. There is no indication or specific teaching in Levy that 100% of the detergent used in the emulsion is washed off.

24. Applicant argues that O'Hagan and Van Nest do not make up for the deficiencies of Levy and for this reason, claims 34-44 and 58-76 are patentable over Levy in view of O'Hagan or Van Nest.

25. Response: The examiner has carefully considered applicant's arguments against Levy as art against the claims and has fully responded to the arguments above. O'Hagan and Van Nest were not applied to cure the deficiencies of Levy enumerated by applicant, but O'Hagan was relied upon for CTAB with PLG and Van Nest for polynucleotide delivery in liposomes and emulsions made with CTAB or DOTAP. Thus, claims 34-42 and 62-76 are not patentable over Levy in view of O'Hagan or van Nest.

26. Applicant cites paragraph [0011] of the instant specification as teaching that the presence of detergent is necessary for adsorption of the biologically active macromolecule to the micro-particle.

27. Response: Levy does not say that the micro-particles are devoid of detergents used in the formation of the micro-sphere. Secondly, the polymer and macromolecules are the same for the claims as well as for the prior art so that conditions necessary for adsorption would be the same in the presence of detergent. 10-90% of the detergent used is a broad range compared to Levy's

absent disclosure that 100% of the 20% detergent used is washed off. Further, Levy also contemplates an embodiment without a wash cycle.

28. Applicant has also cited Example 4 of the instant specification as having loading efficiency of 91% PCMVp55gag plasmid DNA onto washed PLG-PVA micro-particles whereas, in O'Hagan, the loading efficiency on washed PLG-PVA micro-particles for pCMVgp120 plasmid DNA is 44%; Example 7 of O'Hagan has loading efficiency of 84% on PLG-CTAB particles while Example 7 of the instant specification using unwashed PLG-CTAB has a loading efficiency of about 100%.

29. Response: The claims have not recited any loading efficiency of pCMVp55gag plasmid DNA. The fact that O'Hagan has some loading efficiency does not support applicant's assertion that the CTAB would have been expected to interfere with DNA loading. Example 7 of O'Hagan studies the adsorption between PLG-PVA and PLG-CTAB.

30. No claim is allowed.

31. **THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event,

however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

32. Any inquiry concerning this communication or earlier communications from the examiner should be directed to BLESSING M. FUBARA whose telephone number is (571)272-0594. The examiner can normally be reached on Monday to Thursday from 7 a.m. to 5:30 p.m.

33. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Hartley can be reached on (571) 272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

34. Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Blessing M. Fubara/
Primary Examiner, Art Unit 1618